Chronic Myeloid Leukemia

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Updates:
- Longer follow up on IRIS data
- Guidelines for monitoring and definitions of response
- Second generation TKI's

Introduction

Chronic myeloid leukemia (CML) is a clonal hematologic malignancy, which is a relatively rare cancer with an estimated incidence of 1–2 cases per population of 100,000. It represents about 15% of all cases of leukemia in Canada and this incidence is similar in all countries worldwide [1, 2]. Based on this incidence and Canadian cancer statistics, about 550 new cases of CML are estimated to be diagnosed annually in Canada. Median age at diagnosis is 45–55 years with male to female ratio (1.35:1).

CML is characterized by the presence of the ***Philadelphia chromosome (Ph),*** which arises from a balanced translocation between chromosomes 9 and 22. This translocation results in the fusion of the ABL gene on chromosome 9 with the BCR gene on chromosome 22. The resulting BCR-ABL fusion protein is a constitutively active tyrosine kinase, conferring enhanced proliferative activity and decreased sensitivity to apoptotic cell death in the cells in which it is expressed [3]. Depending on the breakpoint on BCR, three oncoproteins may be produced:

(1) **p210** BCR-ABL, which is associated with 98% or more of the cases of Ph-positive chronic myelogenous leukemia (CML); and 20-40 % of Ph-positive acute lymphocytic leukemia (ALL)

(2) **p190** BCR-ABL, which is associated with 60-80% of cases of Ph-positive ALL

(3) **p230** BCR-ABL, which is associated with rare cases of CML (typically good prognosis, indolent) and chronic neutrophilic leukemia (CNL).

Diagnosis

CML typically presents with leukocytosis, a profound left-shift in WBCs, thrombocytosis, and splenomegaly [4], although more commonly today is diagnosed on a routine blood test. The differential diagnosis includes other myeloproliferative disorders, chronic myelomonocytic leukemia, and chronic neutrophilic leukemia. The diagnosis of CML is confirmed by demonstration of the Philadelphia chromosome, t(9;22), on bone marrow and/or peripheral blood samples. This may be achieved by conventional cytogenetics, fluorescence in-situ hybridization (FISH), or polymerase chain reaction (PCR) in either marrow or blood [5].

Baseline Investigations

The CCGM-CML 2006 guidelines recommend the following investigations at diagnosis for all patients with suspected or confirmed CML:

1. Assessment of prognosis (Sokal score see below)
2. Bone marrow aspirate and biopsy (% blasts, % basophils, presence of fibrosis)
3. Baseline bone marrow cytogenetics (to assess for clonal evolution)
4. Peripheral blood or bone marrow for FISH of t(9;22)
5. Peripheral blood or bone marrow Q-RT-PCR for BCR-ABL

*Original treatment policy prepared by Dr. Kevin Imrie with input from Dr. Hans Messner & Dr. Jeffrey Lipton (PMH)
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Initial staging investigations should also include:

- CBC, differential, blood film
- Serum electrolytes, liver function tests, uric acid
- Imaging for spleen size
- HLA testing in all potentially eligible patients

Staging & Prognosis

The Sokal and Hasford prognostic scoring systems have been derived for predicting prognosis in patients with CML. They are both based on clinical and laboratory data obtained at the time of diagnosis. Scores obtained after therapy initiation are less reliable. No prognostic scoring system has been specifically designed for patients on imatinib mesylate, although the Sokal and Hasford systems have both been used in major clinical trials of imatinib therapy; the Sokal system appears to have gained wider acceptance [6, 7].

The Sokal score can be calculated for individual patients by accessing the web site http://www.roc.se/sokal.asp.

The clinical course of CML is typically divided into three phases defined as follows [8]:

A. Chronic Phase	B. Accelerated Phase	C. Blast Phrase
No significant symptoms No features of accelerated or blast phase	Blasts 10-19% of WBC in PB or BM PB basophils ≥ 20% Persistent thrombocytopenia <100 Increasing spleen size or WBC unresponsive to therapy Cytogenetic evidence of clonal evolution	Blasts ≥ 20% in PB or BM Extramedullary blast proliferation Large foci of blasts in BM

Treatment of Chronic Phase

Treatment of CML is aimed at controlling the excessive proliferation of myeloid cells as well as slowing or preventing CML progression. There are several first-line treatment options available in Canada, current treatment options as recommended by The CCGM-CML (2007) include [9]:

1. Targeted drug therapy (kinase inhibitors, imatinib)
2. Allogeneic stem cell transplant (SCT)
3. Chemotherapy (hydroxyurea)
4. Clinical trials with new agents

Hydroxyurea

Hydroxyurea is the drug of choice for the initial reduction of WBCs in CML. Used in isolation, it is associated with a high hematologic response rate and a very favorable toxicity profile [10]. It is not however associated with a significant cytogenetic response rate and it has a fairly limited impact on the long-term prognosis of CML. The favorable toxicity profile makes hydroxyurea a reasonable choice in patients pursuing palliative management. Major toxicities include myelosuppression, mucositis, and leg ulcers.

Dosing: Hydroxyurea is started at a dose of up to 500 - 4000 mg/day and is then titrated to the minimum dose required to maintain a WBC of < 10 $x10^9$/L.

Imatinib (Gleevec®)

Imatinib (Gleevec®) is the only BCR-ABL tyrosine kinase inhibitor indicated for first-line treatment of CML in Canada. It is considered the standard treatment in the US since FDA approval in 2001. The goal of treatment is to reduce the number of cells containing the Ph chromosome.

A phase III study (the IRIS study) compared prospectively the administration of imatinib 400 mg daily to the combination of interferon-alfa and cytarabine in previously untreated patients with CML in chronic phase. Approximately 1100 patients were recruited from 16 countries. Preliminary results were published in 2003 with a median follow-up of 19 months. The estimated rates of complete hematologic response (CHR) for patients whose initial treatment was imatinib were 96%; major cytogenetic response (MCyR), 87%; and complete cytogenetic response (CCyR), 76%. The term MCyR includes both CCyR and partial cytogenetic responses. The results of this study were updated in 2006 with 5-year follow-up [11] and at ASH 2007 with 6-year follow-up [12].

The estimated cumulative rates of CHR and CCyR were 98% and 82% respectively and PFS, EFS and OS were 93%, 83% and 88% respectively. At six years, 66% of the initial 553 patients randomized to imatinib remained on drug. The annual rates of all events as well as progression to accelerated phase or blast crisis declined after the second year of treatment. The estimated annual rate of treatment failure after the start of imatinib was 3.3% year 1, 7.5% year 2, 4.8% year 3, 1.5% year 4, 0.8% year 5 and 0.4% year 6. The time to achievement of complete cytogenetics response did not affect long term outcomes, however long term overall survival was significantly worse for patients who did not achieve a complete cytogenetics remission (6 yr OS 66%)[13].

Time Intervals to achieve a complete cytogenetics remission (CCR) [11]

Time intervals to achieve CCR (n=509)	N	%	OS @ 6y %	PFS@ 6y %	EFS @ 6y %
≤ 6 months	265	52	94	97	93
> 6 to ≤ 12 months	99	19	95	97	90
> 12 to ≤ 18 months	34	7	91	97	87
> 18 months	49	10	98	98	89
No CCR while on imatinib	62	12	63	63	33

Dose: The recommended starting dose of imatinib in the IRIS study was 400 mg daily regardless of the size of the patient, and this remains the standard dose. Higher starting doses of imatinib have been investigated with some evidence of more rapid hematologic, cytogenetic and molecular responses [14].

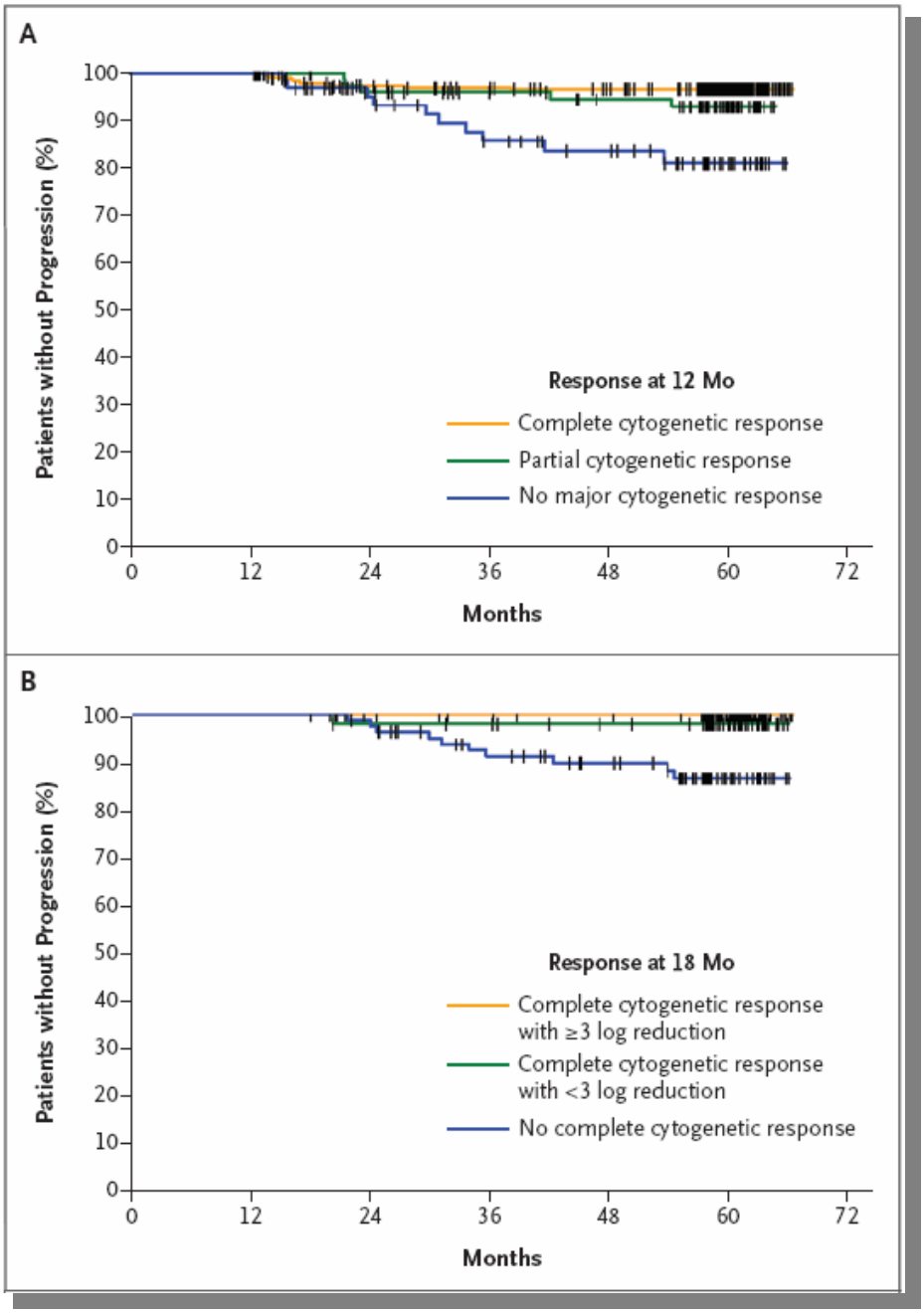
Currently, there is no definite evidence that starting treatment with doses greater than 400 mg daily or escalating dosage for patients who appear to be responding is associated with reduced risk of disease progression or prolonged survival. Increased dosing may overcome resistance due to overexpression or amplification of BCR-ABL in poorly responding patients [15]. In the IRIS trial, dose escalation was recommended for patients who did not achieve a complete hematologic remission by 3 months or a minor cytogenetics remission by 12 months. Nineteen percent of imatinib patients had dose escalation to 600-800 mg/day with a median time to dose escalation of 22 months and at a median dose delivered of 600 mg. With dose escalation, 86% achieved the hematologic response they had either missed or lost and 38% achieved the cytogenetics remission they had either missed or lost at 12 months [16].

Adverse effects: The most common non-hematologic side effects with imatinib are fluid retention and edema (commonly peri-orbital) (55% of patients), nausea (47%), diarrhea (33%), skin rash (30-40%) and muscle cramps (38%). Most are grades 1-2. Congestive heart failure/LV dysfunction (0.7%) and pleural effusions have been observed, but their association with imatinib is uncertain. Other side effects may include hepatotoxicity (3-6%), fatigue (common early). Serious adverse effects are very rare. Low dose diuretics may be useful for edema, antihistamines and topical corticosteroids for skin rash, anti-nauseants for nausea [17].

Adverse hematologic events due to myelosuppression are commonly seen early in CML treatment with imatinib, because imatinib targets BCR-ABL before normal hematopoiesis can be restored [18]. Grades ¾ neutropenia may be seen in 12.3/3.1%, grades ¾ thrombocytopenia in 8.3/0.2% and grades ¾ anemia in 3.1/0.9%) [11]. All toxicities may be managed with dose decrease or discontinuation briefly. Imatinib should

be interrupted if ANC < 1.5 x 10^9/L and PLT count < 50 x 10^9/L. Rarely, Neupogen or erythropoietin may be used for recurrent or persistent grades ¾ toxicities.

How Long? There is preliminary evidence that the incidence of disease progression in responders diminishes with each successive year on imatinib. Moreover, there is no evidence that the incidence of toxicity increases with duration of treatment. Anecdotal evidence suggests that most patients who stop taking imatinib lose their response within weeks or months of discontinuation [19, 20]. These facts taken together suggest that the best advice for individual patients responding to imatinib is that the drug should be continued indefinitely, at the dose that yielded the best response.



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Hematologic Monitoring after Initiation of Imatinib

- If WBC < 20 x 10^9/L, treat with imatinib alone
- If WBC > 20 x 10^9/L, treat with imatinib alone +/- consideration of hydroxyurea, allopurinol, hydration
- **Expected results:** WBC fall by < 2 weeks with normalization by 4-6 weeks; platelets, decrease 1-2 weeks with normalization at 4-6 weeks.

Assessment of Response

Response to treatment in patients with CML typically proceeds in an orderly manner.

- Restoration of spleen size to normal
- Normalization of the blood counts
- Reversion of the bone marrow to Ph negativity on classic cytogenetics (cytogenetics response)
- Reduction in the number of BCR-ABL transcripts in the blood and marrow to very low or undetectable (major or complete molecular response)

Below are definitions of hematological, cytogenetic and molecular response in CML [17]

Complete Hematological Response (CHR)	Partial Hematological Response
WBC <10 x 10^9/L with normal differential Platelets <450 x10^9/L Differential: No immature granulocytes and < 5% basophils	WBC <10 x10^9/L, but with immature forms Reduction of palpable splenomegaly or platelets by ≥ 50% This is a historical category with no clinical utility. Partial hematologic response should be considered equivalent to no response.

Cytogenic Response	Ph-positive Metaphases
Complete: 0% (CcyR) Partial: ≤35% Major – complete plus partial Minor: ≤ 65% Minimal: ≤95%	0% Ph+ metaphases (transcripts not detectable) 1%-35% Ph+ metaphases 0-35% 36%-65% Ph+ metaphases 66%-95% Ph+ metaphases

Complete Molecular Response	Major Molecular Response
No BCR-ABL transcripts detectable with quantitative real time PCR	> 3 log reduction in BCR-ABL transcripts detected with quantitative real time PCR (Major: 0.1%)

It has been observed that the most important marker of a good prognosis in patients on imatinib is achievement of a major molecular response [21]. A major molecular response (MMR) is equivalent to a 3-log reduction from a standardized baseline value of 100%. This is typically achieved when the BCR-ABL level falls approximately 1 log below the level at which a CCR is achieved. The terms "transcripts not detected" and "transcripts not detectable" are preferred to "complete molecular response" (sometimes referred to as CMR). [22].

For those patients achieving this by 12 months, the probability of remaining free of progression to advanced phase at 5 years of imatinib treatment was 100% [11].

Monitoring Response to Treatment

Monitoring

The CCGM-CML recommends that patients be monitored every 3 months for toxicity of treatment as well as response by Q-RT-PCR or FISH, with any decisions to alter therapy based on achieving set milestones.

Milestone Criteria, Definitions and Timelines

Response	Duration of Therapy
CHR: Complete hematologic response	3 months
Any cytogenetic response	6 months
MCR: Major cytogenetic response	12 months
CCR: Complete cytogenetic response	18 months
MMR: Major molecular response	24 months

Imatinib Resistance or Intolerance

Definitions of Imatinib resistance in CP CML [9, 17, 23]

Primary Resistance

Failure to meet the following milestones:

- CHR at 3 months
- Any cytogenetic response at 6 months
- MCR at 12 months
- Patients who have failed to meet the above milestones at 400 mg po qd and are not able to tolerate 800 mg/day

Secondary Resistance

- Molecular relapse (persistent transcript increase of > 0.5 log)
- Cytogenetic relapse (change in class or any Ph+ cell increase > 30%)
- Loss of CHR

Definitions of Imatinib Resistance in AP/BC

Primary Resistance

- Lack of response following > 4 weeks at > 600 mg/day
- Failure to achieve CHR in AP or CHR/no evidence of leukemia in BC at 3 months

Secondary Resistance

- Molecular relapse (persistent transcript increase of > 0.5 log)
- Cytogenetic relapse 9 change in class or any Ph+ cell increase to > 30%
- Loss of CHR

Definition of Imatinib Intolerance

- Grade 3 non-hematologic toxicity lasting > 7 days
- Grade 4 hematologic toxicity lasting 7 days
- Any sustained grade 2, symptomatic non-heme toxicity lasting > 30 days

Approximately 15-20% of patients with newly diagnosed CML do not achieve a complete cytogenetics response to imatinib. A small number have side effects that prevent further treatment with the drug and a small number have an initial cytogenetic response, but relapse with a Ph-chromosome recurrence, often heralded by a rise in the BCR-ABL transcript number. In all patients with suboptimal responses or treatment failure it is important to confirm that the patient is taking the imatinib as prescribed. A serum level may be checked if doubt remains as there is data demonstrating that a plasma threshold of 1002 ng/ml is the optimal trough imatinib plasma level predictive of complete cytogenetics and major molecular responses [24]. Patients with levels less than target might benefit from increased dosing to 800 mg daily [16].

There is no consensus how to manage a patient who achieves a CCyR but who do not achieve > 3 log reduction in BCR-ABL transcript numbers. The options include making no change in imatinib dosage, increasing imatinib to 600 mg or 800 mg daily, or switching to a novel tyrosine kinase inhibitor **(discussed below)**.

Mutational Analysis

Patients who fail treatment with imatinib, or have suboptimal responses or rising transcripts of BCR-ABL should be screened for the presence of kinase domain mutations, including those at residues Y253, E255 and T315I. These patients are unlikely to respond to imatinib and should be considered for allogeneic transplant or other tyrosine kinase inhibitors (with exception of T315I which does not respond to dasatinib or nilotinib) [25-28]. Additionally, these patients should be screened for additional cytogenetics abnormalities in the Ph-positive clone which may be detected in up to 58% of imatinib resistant patients [29].

Alternative Therapies in Imatinib Failures

Patients who fail imatinib and are ineligible for transplantation should be offered dasatinib or nilotinib, both novel BCR-ABL-1 inhibitors that have significant activity against the BCR-ABL1 kinase domain mutations and BCR-ABL1 overexpression, the two most common mechanisms of imatinib resistance **(see below)**. For those with possible matched donors, no firm recommendations can yet be made. One possible compromise is to administer a second-generation TKI for a finite period (e.g. 6 or 9 months) and to proceed with an allogeneic stem-cell transplantation in the absence of a durable response.

The pharmacokinetic properties of imatinib, dasatinib and nilotinib are compared in the table below

	Imatinib	Dasatinib	Nilotinib
Administration	Oral	Oral	Oral
Potency	1	300	30
T1/2 (hours)	20	5.5	15
Dose	400 mg qd	100 mg qd	400 mg bid
Resistance	> 70, T3151	T3151	T3151
Major side effects	Cytopenias; fluid retention; MSK; diarrhea: rash	Cytopenias, pleural effusion, GI bleeding, Q-Tc prolongation	Cytopenias; lipase/amylase, bilirubin: Q-Tc prolongation

Dasatinib

Dasatinib is an orally available multi-targeted kinase inhibitor that differs from imatinib in that it can bind both to the active and inactive conformations of the **Abl kinase** domain and also inhibits **Src family** kinases, PDGFR, c-Kit and ephrin A receptor kinases. Thus, it has been referred to as a dual inhibitor.

It is approximately 300 times more active than imatinib and in vitro is active against most of the imatinib-resistant mutant subclones, ***with the notable exception of the T315I clone*** [30] and probably also of ***a F317L mutant clone*** [31]. Thus far, the drug has been used predominantly in CML patients judged to be resistant to or intolerant of imatinib [30]. In a phase II study of 387 patients with imatinib-resistant or

imatinib-intolerant CML who received dasatinib at 70 mg po bid daily, CHR were achieved in 90% of patients; MCR were seen in 62% of evaluable patients (55% imatinib resistant, 82% imatinib intolerant), CCR in 53% and MMR in 47% [32]. CCR Responses were maintained in 95% of the responding patients. Overall, PFS was 80% at 2 years (94% for imatinib resistant) and OS was 94% (100% if imatinib intolerant). Patients with T315I mutations proved resistant [33]. Dasatinib also has activity in accelerated phase CML resistant to or intolerant of imatinib achieving MHR in 63%; CHR in 45% MCR in 39%, CCR in 32% [34]. In the Start-R trial, dasatinib 70 mg po bid was compared in a 2:1 randomization with imatinib 800 mg/day in patients resistant to prior imatinib 400-600 mg po daily. MCR rates were higher with dasatinib (53% versus 33% respectively, p=.017), the CCR rate with dasatinib was more than double that of imatinib (44% versus 18%, P=.0025) and the MMR was higher (29% versus 12%, p=.0028) [35, 36]. Time to treatment failure was also higher in the imatinib treated patients. In another trial, the most favorable PFS in different dasatinib dosing regimens was 100 mg po daily and is the recommended starting dose [31]. The use of dasatinib in CML was approved in 2006 by FDA in the United States and the European Agency for the Evaluation of Medical Products (EMEA) in Europe [30]. Approval in Canada was obtained in April 2007.

Side effects to Desatinib in CP CML include: pleural effusions (27%; grades 3-4 6%), peripheral edema (18%), pericardial effusion (4%), CHF (5%) neutropenia (grade 3-4 48%), thrombocytopenia (grade 3-4 48%), anemia (grades 3-4 18%) diarrhea, vomiting, nausea, gastrointestinal hemorrhage, and rashes [32]. Of particular interest has been the occurrence in some patients of pleural and pericardial effusions, most of which resolved when the drug was stopped. Risk factors for pleural effusions include prior rash on imatinib, history of prior autoimmune disease, higher dose and hypercholesterolemia [30]. Dose interruptions and reductions are common with dasatinib (61% and 43% respectively) [32].

Nilotinib

Nilotinib is a more potent selective inhibitor of BCR-ABL1 auto or messenger phosphorylation than imatinib. There are sizable phase 2 trials ongoing and reported in abstract form in both chronic and accelerated phase CML who are resistant to or intolerant of imatinib. At ASH 2007, the reported CHR was 77% and CCR 41% (84% sustained for 18 months) for patients with CP CML resistant to or intolerant of imatinib (n=321) [37]. Nilotinib also has significant activity in patients with AP CML resistant or intolerant to imatinib 55% with mutations at baseline (CHR 54%; MCR 31%, CCR 19%) [38]. Nilotininb may also have activity in patients with CP, AP or BC CML who are dasatinib failures [39]. The chief toxicities are hematologic (50% anemia, 9% grades 3-4, neutropenia 52%, grades 3-4 30%; thrombocytopenia 61%, grades 3-4 33%). [40]. Fortunately, grades 3-4 biochemical abnormalities are uncommon in CP CML (< 15%), but grades 1-2 liver enzyme abnormalities are common. Rash is seen in 34%, diarrhea in 25%, headache 32%, nausea 33%, fatigue 29%, pruritus 30% - but all are largely grades 1-2. Grades 3-4 AEs associated with fluid retention were rare in patients with either CP or AP CML [38, 40].

Allogenic Stem Cell Transplantation (AlloSCT)

Until the advent of imatinib, it was standard care to offer young patients with newly diagnosed chronic-phase CML treatment with high-dose chemotherapy or chemoradiotherapy followed by allogeneic hematopoietic stem cell transplant from HLA-identical siblings, family members, or HLA-matched unrelated donors. Only about 10% of CML patients were eligible for the procedure for logistical and age-related reasons. Given the up front morbidity and mortality of this approach, and the new era of imatinib therapy, allogeneic transplant is rarely offered as front-line therapy, however it may still be appropriate to consider for young patients with higher risk disease, for those not in remission or in hematologic relapse after 3 months following primary treatment with imatinib, for those who have no cytogenetic response or those in cytogenetic relapse at 6, 12 or 18 months after achieving initial hematologic remission, especially those with a T3151 mutation [17].

Allogeneic transplantation using unrelated HLA-compatible donors is associated with significant morbidity and mortality. Risk factors for MUD transplant related mortality include: Age (>35 years), advanced disease, prolonged interval from diagnosis to transplantation, cytomegalovirus seropositivity, and extent of HLA disparity. Patients with none of these risk factors have been reported to have a five-year survival as high as 61% in one prospective cohort study [41]. Patients must be made aware of the risks and profound effect on quality of life before considering this option.

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Interferon Alpha (IFN)

The introduction of imatinib has entirely replaced the use of interferon-alfa as primary treatment for CML in chronic phase. However, for the patient who achieved CCyR on interferon-alfa in the 1990's and maintains stable minimal residual disease, switching to Imatinib or continuing interferon is controversial, and no useful recommendations can be offered. Major side effects include influenza-like syndrome (25%), gastrointestinal symptoms (15%), and other toxicities in less than 10% (hematologic, hepatic, neurologic, dermatologic, and psychiatric). Interferon has not been studied in patients over the age of 70 years. The side effects of interferon appear to increase with age. The use of IFN for second-line therapy is now virtually obsolete with second generation kinase inhibitors available.

Odette Cancer Centre Policy (First-line Therapy)

- The newly diagnosed patient with CML
  - Hydroxyurea may be used initially for disease stabilization if WBC is > 20 x 10^9/L
  - Imatinib dose based on disease stage
    - Chronic phase 400 mg daily
    - Accelerated phase 600 mg daily
    - Blast crisis up to 800 mg daily

- Patients should be monitored for response every 3 months for cytogenic and molecular response
- Patients should undergo yearly bone marrow assessment of cytogenetics

- Patients under age 70 should undergo HLA testing. Searches should be considered for those without matched siblings. Those with an HLA-compatible donor should be seen at PMH in consultation to discuss the relative merits of allogeneic BMT. In general, alloBMT will be considered in patients at low risk of transplant related mortality (young age, 6/6 related match) and/or those at high risk of progression to accelerated phase. AlloBMT should be performed within 12-24 months of diagnosis. Ultimately however, patient preference will guide decision-making.

- Slow responders on imatinib should have their dose escalated to 600 mg or 800 mg per day

- Patients on imatinib who fail to respond, have hematologic progression, or have cytogenetic progression (loss of complete cytogenetic response), should be offered Dasatinib 100mg daily or nilotinib 400 mg po bid and/or be considered for allogeneic stem cell transplant or offered enrollment in clinical trials if available.

Management of Accelerated Phase

Approximately 82% of imatinib-naïve, accelerated phase CML patients will achieve a hematologic response, and 24% will achieve a major cytogenetic response with imatinib [42]. Patients with accelerated phase CML on imatinib and progressive disease **(see above)** should be switched to a second generation TKI. However, responses tend to be short-lived with 4 year survival 40% [43]. Patients eligible for allogeneic transplantation should be referred for consultation early after acceleration is diagnosed.

Management of Blast Crisis

Blast crisis is defined as 30% or greater blasts in the blood, bone marrow or both or as the presence of extramedullary disease [8]. Patients with blast crisis have a poor prognosis. Imatinib 800 mg/day (400 mg BID) can be used in patients with projected median survival of 4.9 months and 4 year survival of 10% [15]. Patients eligible for allogeneic transplantation should be offered aggressive therapy including induction chemotherapy. Patients not eligible for transplantation should be managed with second generation TKI's, or on experimental protocols or conservatively with palliative intent [44].

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